PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 487/04, A61K 31/5517, C07B 61/00, G01N 33/50 // (C07D 487/04, 243:00, 209:00)

A3

(11) International Publication Number: WO 00/12509

(43) International Publication Date: 9 March 2000 (09.03.00)

(21) International Application Number: PCT/GB99/02839

(22) International Filing Date: 27 August 1999 (27.08.99)

(30) Priority Data:
9818732.1 27 August 1998 (27.08.98) GB

(71) Applicant *(for all designated States except US)*: THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION [GB/GB]; University House, Winston Churchill Avenue, Portsmouth PO1 2UP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: THURSTON, David, Edwin [GB/GB]; University of Portsmouth, St Michael's Building, White Swan Road, Portsmouth, Hampshire PO1 2UP (GB). HOWARD, Philip, Wilson [GB/GB]; University of Portsmouth, St Michael's Building, White Swan Road, Portsmouth, Hampshire PO1 2DT (GB).

(74) Agents: WATSON, Robert, J. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

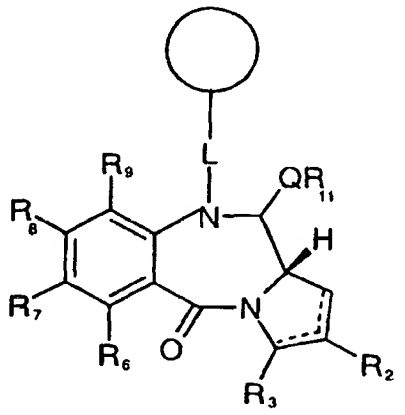
(88)Date of publication of the internationl search report:
06 July 2000 (06.07.00)

Date of publication of the amended claims:
10 August 2000 (10.08.00)

(54) Title: COLLECTIONS OF COMPOUNDS

(57) Abstract

A compound of formula (I), wherein: R_2 and R_3 are independently selected from H, R, OH, OR, =0, =CH–R, $=CH_2$, CH_2–CO_2R, CH_2–CO_2H, CH_2–SO_2R, O–SO_2R, CO_2R, COR and CN, and there is optionally a double bond between C1 and C2 or C2 and C3; R_6, R_7, R_8 and R_9 are independently selected from H, R, OH, OR, halo, nitro, amino, Me_3Sn; R_{11} is either H or R; Q is S, O or NH; L is a linking group, or a single bond; O is a solid support; or where one or more of R_2, R_3, R_6, R_7 and R_8 are independently: H–$(T)_n$–X–Y–A– where: X is CO, NH, S or O; T is a combinatorial unit; Y is a divalent group such that HY = R; A is O, S, NH, or a single bond and n is a positive integer.



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AMENDED CLAIMS

[received by the International Bureau on 29 June 2000 (29.06.00); original claim 17 amended; remaining claims unchanged (1 page)]

is present, are independently selected from lower alkyl group having 1 to 10 carbon atoms optionally substituted by one or more halo, hydroxy, amino, or nitro groups.

11. A compound according to claim 10, wherein R, and HY, if Y is present, are unsubstituted straight or branched chain alkyl groups, having 1 to 10 carbon atoms.

12. A compound according to any one of the preceding claims, wherein Q is O.

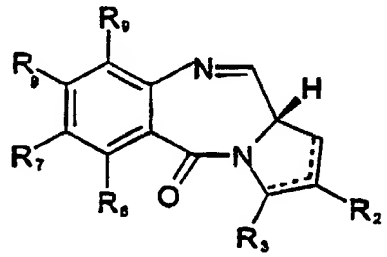
13. A compound according to any one of the preceding claims, wherein R_{11} is H.

14. A compound according to any one of the preceding claims, wherein R_6 and R_9 are H.

15. A compound according to any one of the preceding claims, wherein R_7 is an alkoxy group.

16. A compound according to any one of the preceding claims, wherein R_2 and R_3 are H.

17. A compound of formula II:



(II)

wherein R_2, R_3, R_6, R_7, R_8 and R_9 are as defined in any one of claims 2 to 16.

18. A compound of formula II as defined in claim 17 for use in a method of therapy.

19. A pharmaceutical composition, comprising a compound of

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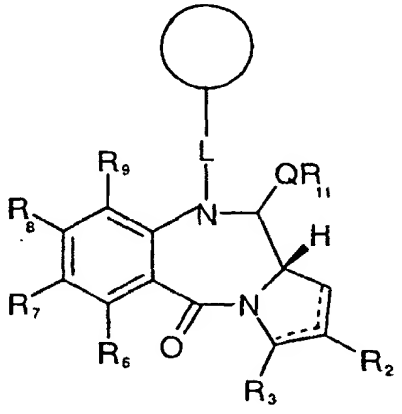
Published

Without international search report and to be republished upon receipt of that report.

(54) Title: COLLECTIONS OF COMPOUNDS

(57) Abstract

A compound of formula (I), wherein: R_2 and R_3 are independently selected from H, R, OH, OR, =O, =CH–R, $=CH_2$, CH_2–CO_2R, CH_2–CO_2H, CH_2–SO_2R, O–SO_2R, CO_2R, COR and CN, and there is optionally a double bond between C1 and C2 or C2 and C3; R_6, R_7, R_8 and R_9 are independently selected from H, R, OH, OR, halo, nitro, amino, Me_3Sn; R_{11} is either H or R; Q is S, O or NH; L is a linking group, or a single bond; O is a solid support; or where one or more of R_2, R_3, R_6, R_7 and R_8 are independently: $H–(T)_n–X–Y–A–$ where: X is CO, NH, S or O; T is a combinatorial unit; Y is a divalent group such that HY = R; A is O, S, NH, or a single bond and n is a positive integer.



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13. A compound according to any one of the preceding claims, wherein R_{11} is H.

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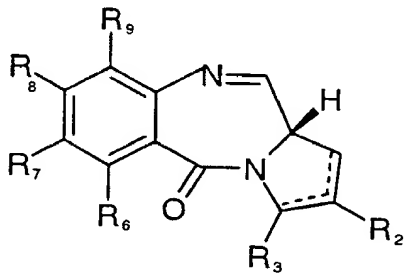
16. A compound according to any one of the preceding claims, wherein R_2 and R_3 are H.

17. A compound of formula **II**:



(II)

wherein R_2, R_3, R_6, R_7, R_8 and R_9 are as defined in any one of claims 1 to 16.

18. A compound of formula **II** as defined in claim 17 for use in a method of therapy.

19. A pharmaceutical composition, comprising a compound of

formula **II** as defined in claim 17, and a pharmaceutically acceptable carrier or diluent.

20. The use of a compound of formula **II** as defined in claim 17 in the preparation of a medicament for the treatment of a gene-based disease.

21. The use of a compound of formula **II** as defined in claim 17 in the preparation of a medicament for the treatment of bacterial, parasitic or viral infections.

22. A collection of compounds all of which are represented by formula **I** as defined in any one of claims 1 to 16.

23. A collection of compounds all of which are represented by formula **II** as defined in claim 17, wherein R_2, R_3, R_6, R_7 and R_8 are as defined in any one of claims 4 to 8, or in any one of claims 9 to 11, 14, 15, or 16 as appendant, directly or indirectly, on any one of claims 4 to 8.

24. A method of screening a collection of compounds of formula **II** as defined in claim 17 to discover biologically active compounds.

25. The use of a compound of formula **II** as defined in claim 17 in a method of target validation or functional genomics.

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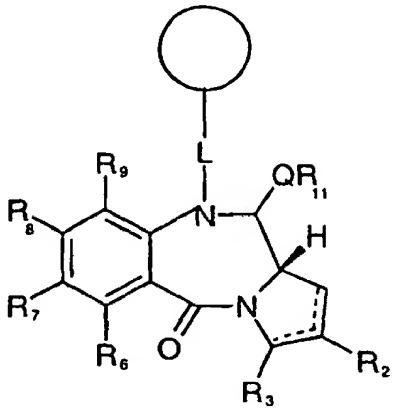

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02839

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/5517 C07B61/00 G01N33/50
//(C07D487/04,243:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BI Y ET AL: "Building blocks for peptide and carbamate libraries" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 6, no. 19, 8 October 1996 (1996-10-08), pages 2299-2300, XP004135826 ISSN: 0960-894X	1
X	US 4 239 683 A (ARAKAWA YOSHIO ET AL) 16 December 1980 (1980-12-16) column 1, line 32 -column 2, line 11; table 2	17,18
X	FR 2 586 683 A (CENTRE NAT RECH SCIENT) 6 March 1987 (1987-03-06) claims 1,17	17,18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2000	03/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[redacted]nal Application No
PCT/GB 99/02839

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 98, no. 9, 1983 Columbus, Ohio, US; abstract no. 72145x, FUJISAWA: "Benzodiazepine derivatives" page 638; XP002136017 abstract & JP 57 131791 A (FUJISAWA) 14 August 1982 (1982-08-14)	17,18
X	CHEMICAL ABSTRACTS, vol. 99, no. 17, 1983 Columbus, Ohio, US; abstract no. 139983k, FUJISAWA: "Benzodiazepine derivatives" page 603; XP002136018 abstract & JP 05 841884 A (FUJISAWA) 11 March 1983 (1983-03-11)	17,18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 99/02839

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 18 to 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]on on patent family members

[redacted]nal Application No
PCT/GB 99/02839

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4239683 A	16-12-1980	JP 1175707 C	14-11-1983
		JP 54090195 A	17-07-1979
		JP 58005916 B	02-02-1983
		DE 2844292 A	28-06-1979
		US 4185016 A	22-01-1980
FR 2586683 A	06-03-1987	NONE	
JP 57131791 A	14-08-1982	JP 1592250 C	14-12-1990
		JP 2016315 B	16-04-1990
JP 5841884 A		NONE	

REC'D 15 NOV 2000
WIPO PCT

PATENT COOPERATION TREATY

PCT

15

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RJW/LP5791934		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/02839	27/08/1999	27/08/1998
International Patent Classification (IPC) or national classification and IPC C07D487/00		
Applicant THE UNIVERSITY OF PORTSMOUTH HIGHER EDUC..et.al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/03/2000	13.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baston, E Telephone No. +49 89 2399 2120

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02839

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-47	as originally filed				
Claims, No.:					
1-10	as originally filed				
11-26	as received on	21/08/2000	with letter of	17/08/2000	
Drawings, sheets:					
1/12-12/12	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26
Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

To section V

The following documents have been taken into consideration for the examination of the present application:

D1: BI Y ET AL: 'Building blocks for peptide and carbamate libraries' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 6, no. 19, 8 October 1996 (1996-10-08), pages 2299-2300, XP004135826 ISSN: 0960-894X

D2: US-A-4 239 683 (ARAKAWA YOSHIO ET AL) 16 December 1980 (1980-12-16)

D3: FR-A-2 586 683 (CENTRE NAT RECH SCIENT) 6 March 1987 (1987-03-06)

D4: CHEMICAL ABSTRACTS, vol. 98, no. 9, 1983 Columbus, Ohio, US; abstract no. 72145x, FUJISAWA: 'Benzodiazepine derivatives' page 638; XP002136017 & JP 57 131791 A (FUJISAWA) 14 August 1982 (1982-08-14)

D5: CHEMICAL ABSTRACTS, vol. 99, no. 17, 1983 Columbus, Ohio, US; abstract no. 139983k, FUJISAWA: 'Benzodiazepine derivatives' page 603; XP002136018 & JP 05 841884 A (FUJISAWA) 11 March 1983 (1983-03-11)

The subject-matter of claims 1-19 (compounds), 20,21 (use), 22,23 (collection), 24 (method) and 25,26 (use) is novel (Art. 33(2) PCT), since no document of the prior discloses compounds of formula I (basically different due to the attachment to the solid support) or II (important differences with respect to the substituents R_6-R_9) and does not anticipate a use for e.g. gene-based diseases.

Claims 1-26 do not involve an inventive step (Art. 33(3) PCT) for the following reason: Documents D2 (column 7, table I), D4 (page 1036, compound 2) and D5 already disclose compounds falling in the scope of general formula I after liberation from the solid support. Thus the attachment and chemical synthesis of these compounds on solid support according to standard techniques (see also D1 and description page 9-13) with the aim of providing e.g. new anti-cancer agents does not render these derivatives inventive. Moreover D1 already states the use of closely related compounds (benzodiazepine derivatives) in the synthesis of combinatorial libraries.

It has to be stated that unlimited expressions like "functional group" or "linking group" which are employed in the claims are not considered appropriate, since a person skilled in the art can only understand these expressions on the basis of explanations given in the description (compare section VIII).

Additionally the discovery of biologically active compounds (claim 24) is per se not considered to involve an inventive step.

To section VIII

The following unlimited expressions are not clear (Art. 6 PCT) and have to be replaced by formulations which reduce the scope of the claims to those congeners, for which evidence is to be found in the description, that they really represent a solution to the problem underlying in the application:
Claim 1: Line 14: "linking group"; line 23 " functional group".
Claim 2: Line 1: "nitrogen protecting group"; line 2: "acid protecting group".
Claim 4: Line 15: "combinatorial unit".

Claim 24 is not clear (Art. 6 PCT), due to the expression "biologically active compound", since any compound per se possesses a biological activity.

Copy for the designated Office (DO/US)

PCT/GB99/02839

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WATSON, Robert, J.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year)
12 April 2000 (12.04.00)

Applicant's or agent's file reference
RJW/LP5791934

International application No.
PCT/GB99/02839

IMPORTANT NOTIFICATION

International filing date (day/month/year)
27 August 1999 (27.08.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
HOWARD, Philip, Wilson
University of Portsmouth
St Michael's Building
White Swan Road
Portsmouth
Hampshire PO1 2DT
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
HOWARD, Philip, Wilson
Cancer Research Campaign
Experimental Cancer Chemo
therapy Laboratories
University of Nottingham
University Park, Nottingham
Nottinghamshire NG7 2RD
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
I. Britel

Telephone No.: (41-22) 338.83.38

003222784

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WATSON, Robert, J.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year)
12 April 2000 (12.04.00)

Applicant's or agent's file reference
RJW/LP5791934

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/02839

International filing date (day/month/year)
27 August 1999 (27.08.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
THURSTON, David, Edwin
University of Portsmouth
St Michael's Building
White Swan Road
Portsmouth
Hampshire PO1 2UP
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
THURSTON, David, Edwin
Cancer Research Campaign
Experimental Cancer Chemo
therapy Laboratories
University of Nottingham
University Park, Nottingham
Nottinghamshire NG7 2RD
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
I. Britel

Telephone No.: (41-22) 338.83.38

003222777

TENT COOPERATION TRE.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 May 2000 (03.05.00)	
International application No. PCT/GB99/02839	**Applicant's or agent's file reference** RJW/LP5791934
International filing date (day/month/year) 27 August 1999 (27.08.99)	**Priority date** (day/month/year) 27 August 1998 (27.08.98)
Applicant THURSTON, David, Edwin et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 March 2000 (17.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WATSON, Robert, J.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year)
12 January 2001 (12.01.01)

Applicant's or agent's file reference
RJW/LP5791934

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/02839

International filing date (day/month/year)
27 August 1999 (27.08.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
THE UNIVERSITY OF PORTSMOUTH
HIGHER EDUCATION CORPORATION
University House
Winston Churchill Avenue
Portsmouth PO1 2UP
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
SPIROGEN LIMITED
79 George Street
Ryde
Isle of Wight P033 2JF
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
I. Britel
Telephone No.: (41-22) 338.83.38

003770851

V0

PATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
RJW/LP5791934		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 02839	27/08/1999	27/08/1998

Applicant

THE UNIVERSITY OF PORTSMOUTH HIGHER EDUC..et.al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/ 02839

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 18 to 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
T/GB 99/02839

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/5517 C07B61/00 G01N33/50
//(C07D487/04,243:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BI Y ET AL: "Building blocks for peptide and carbamate libraries" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 6, no. 19, 8 October 1996 (1996-10-08), pages 2299-2300, XP004135826 ISSN: 0960-894X	1
X	US 4 239 683 A (ARAKAWA YOSHIO ET AL) 16 December 1980 (1980-12-16) column 1, line 32 -column 2, line 11; table 2	17,18
X	FR 2 586 683 A (CENTRE NAT RECH SCIENT) 6 March 1987 (1987-03-06) claims 1,17	17,18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2000	03/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 98, no. 9, 1983 Columbus, Ohio, US; abstract no. 72145x, FUJISAWA: "Benzodiazepine derivatives" page 638; XP002136017 abstract & JP 57 131791 A (FUJISAWA) 14 August 1982 (1982-08-14)	17,18
X	CHEMICAL ABSTRACTS, vol. 99, no. 17, 1983 Columbus, Ohio, US; abstract no. 139983k, FUJISAWA: "Benzodiazepine derivatives" page 603; XP002136018 abstract & JP 05 841884 A (FUJISAWA) 11 March 1983 (1983-03-11)	17,18

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02839

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4239683 A	16-12-1980	JP 1175707 C	14-11-1983
		JP 54090195 A	17-07-1979
		JP 58005916 B	02-02-1983
		DE 2844292 A	28-06-1979
		US 4185016 A	22-01-1980
FR 2586683 A	06-03-1987	NONE	
JP 57131791 A	14-08-1982	JP 1592250 C	14-12-1990
		JP 2016315 B	16-04-1990
JP 5841884 A		NONE	

Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 19, pp. 2299-2300, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00414-3

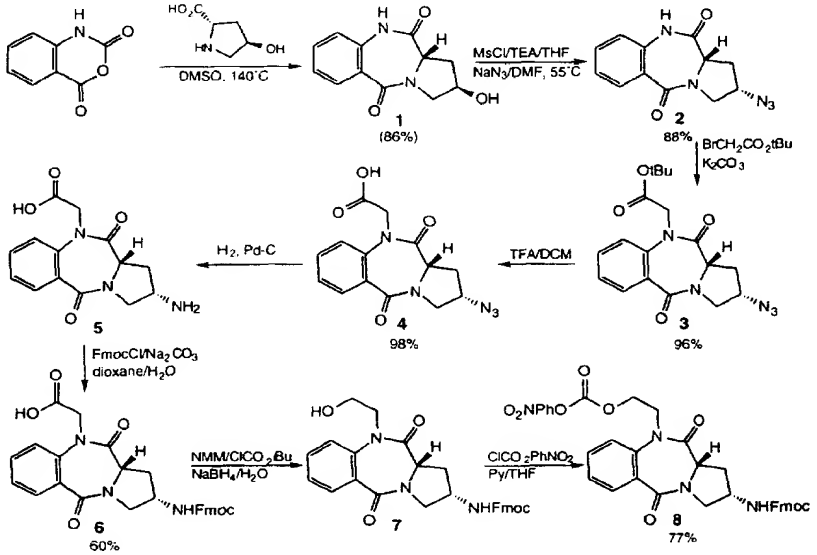
BUILDING BLOCKS FOR PEPTIDE AND CARBAMATE LIBRARIES

Yingzhi Bi and Peter G. Schultz*

Department of Chemistry, University of California, Berkeley, CA 94720

Abstract: A building block containing the 1,4-benzodiazepine-2,5-diazepine pharmacophore has been synthesized for use in constructing both peptide and carbamate combinatorial libraries. Copyright © 1996 Elsevier Science Ltd

Unnatural amino acids have found considerable use as building blocks in medicinal, peptide and protein chemistry,[1] and more recently, in the generation of combinatorial libraries for drug discovery.[2] These include conformationally constrained amino acids, amino acids bearing biophysical probes and photoaffinity labels, and amino acids containing side chain groups with novel steric or electronic properties. Amino acids that incorporate pharmacophores are particularly attractive for the synthesis of combinatorial libraries.[3] The benzodiazepine skeleton has been found in a wide range of biologically active molecules[4,5] and has itself been synthesized in a combinatorial format.[5] We report here the synthesis of Fmoc protected amino acid **6** and amino carbonate **8** building blocks containing the benzodiazepine pharmacophore for use in the synthesis of peptide and carbamate combinatorial libraries.



The dilactam alcohol **1** was chosen as a key intermediate for further elaboration. Amongst the different methods[6-8] reported in the literature for the preparation of 1,4-benzodiazepin-2,5-diones, Kim's

method[6] is the simplest. Thus with a slight modification of the Stille procedure[6b] the desired core skeleton **1** was obtained in 86% yield by reacting isatoic anhydride with *t*-4-hydroxylproline in DMSO at 140 °C. The hydroxyl function was then converted into an azido group in 88% overall yield by mesylation of the hydroxyl group in THF in the presence of TEA followed by azide displacement in DMF at 55 °C. The displacement went exclusively with conversion of the configuration as indicated by the isolation of a single product and confirmed by the splitting pattern and coupling constants of the protons on the adjacent carbons. Alkylation of the amide nitrogen with *t*-butyl bromoacetate followed by removal of the *t*-butyl group with 50% TFA in methylene chloride introduced the acid functionality. Reduction of the azide under hydrogen in the presence of Pd/C catalyst afforded the amino group which was directly protected with Fmoc according to the literature method.[9] Reversal of the above sequence, i.e., reduction of the azide followed by protection of the amino group with Fmoc then the removal of the *t*-butyl group, is also a viable approach. However, the current sequence is more versatile and could be used to generate the Boc amino analogues or any other protected amino analogues. Finally the Fmoc amino acid was converted into the desired carbamate building block in 77% overall yield.[10]

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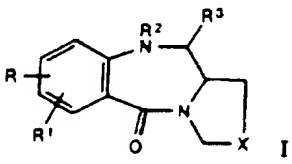
Page: 639

98: 72145x **Benzodiazepine derivatives.** Fujisawa Pharmaceutical Co., Ltd. **Jpn. Kokai Tokkyo Koho JP 57,131,791** [82,131,791] (Cl. C07D487/04), 14 Aug 1982, GB Appl. 80/41,626, 31 Dec 1980; 12 pp. Title compds. I (R = OH; R^1 = alkoxy; R^2 = H; R^3 = alkoxy;



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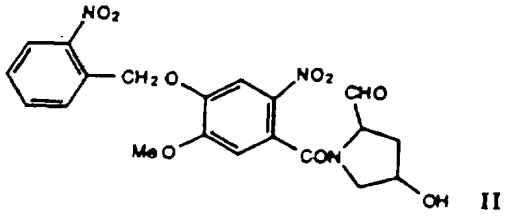
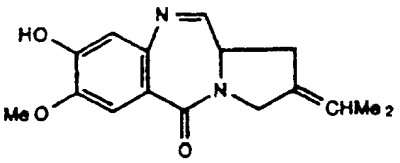


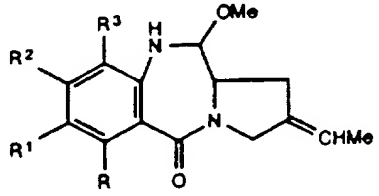
II

R^2R^3 = bond; X = CHOH, S, CO, C:CHCN, C:NR^5, R^5 = alkoxy), useful as bactericides, and antineoplastics (data given), were prepd. Thus, reductive cyclization of pyrrolidine **II** with 10% Pd/C gave **I** (R = 8-OH, R^1 = 7-MeO, R^2R^3 = bond, X = CHOH).

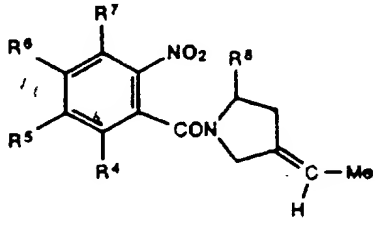
99: 139983k **Benzodiazepine derivatives.** Fujisawa Pharmaceutical Co., Ltd. **Jpn. Kokai Tokkyo Koho JP 58 41,884 [83 41,884]** (Cl. C07D487/04), 11 Mar 1983, Appl. 81/141,502, 07 Sep 1981; 10 pp.



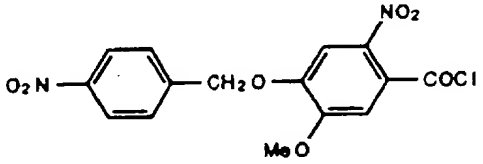
I



II



III



IV

Antibacterial and anticarcinogenic (no data) benzodiazepine derivs. **I** and **II** (R = R^3 = H, R^1 = Me, R^2 = HO; R = R^3 = HO, R^1 = R^2 = H) were prepd. by reductive cyclization of **III** [R^4–R^7 = H, MeO, (protected) HO; R^8 = CHO]. Thus, reaction of *N*-(*tert*-butoxycarbonyl)-4-oxo-L-proline Ph_2CH ester with $EtPh_3PBr$ followed by deprotection gave (4*Z*)-ethylidene-L-proline Ph_2CH ester, whose